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A Very General Solvation Model for BioMolecular Simulation

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A continuum description of solvation for macromolecular structure is presented in the framework of classical molecular mechanics. The essential kernel of the proposed solvation model is similar in spirit to the popular PCM approach frequently used in Quantum Chemistry. However, electronic degrees of freedom are not considered explicitly here and a partial charge discretization is employed instead. The major advantage with such a description is the clear-cut separation into individual physical terms that can all be parameterized independently. Three contributions will constitute the model, a polarization term derived from Poisson Boltzmann theory, a cavitation term obtained from free energy perturbation calculations and a dispersion term using modified Caillet-Claverie coefficients that can be determined from first principle calculations. The model description is very general and can be easily adapted for any kind of solvent considered.

1 Introduction

A proper theoretical description of the native behaviour of BioMolecules will always have to consider effects coming from the environment. Proteins, DNA, RNA, lipids, carbohydrates and all other classes of essential biochemical matter do usually exist and function only in their native environment, i.e. in water, membranes or some other kind of cellular matrix. If we therefore address complex biological behaviour with theoretical methods then we also have to somehow think of appropriate means to account for the environment.

The majority of cases in structural biology usually deals with aqueous systems. Water can be incorporated into theoretical models by either explicit solvation (addition of a shell of molecular water in full atomic detail) or by implicit solvation models (consideration of the environment as a structureless continuum having a specific dielectric constant, i.e. ε = 80 in the case of water). In the following we want to focus on an example of implicit solvation. It is the classical analogon to the very powerful *Polarizable Continuum Method* widely used in the Quantum Chemistry community[1]. Instead of quantum resolution of the electronic degrees of freedom we restrict ourselves to the approximation of atom-centered partial charges taken from the AMBER force field[2]. Because the present description aims at covering non-electrostatic effects too, we would like to term this approach an *Enhanced Implicit Solvation Model*. It is according to the statement used by Dill et. al.[3] a typical BIPSE model, which stands for *Break Into Pieces Sum-up the Energies.* The formal decomposition reads

$$\Delta G^{solv} = \Delta G^{pol} + \Delta G^{cav} + \Delta G^{disp} \tag{1}$$

and each of the individual terms together with their critical aspects shall be discussed next.

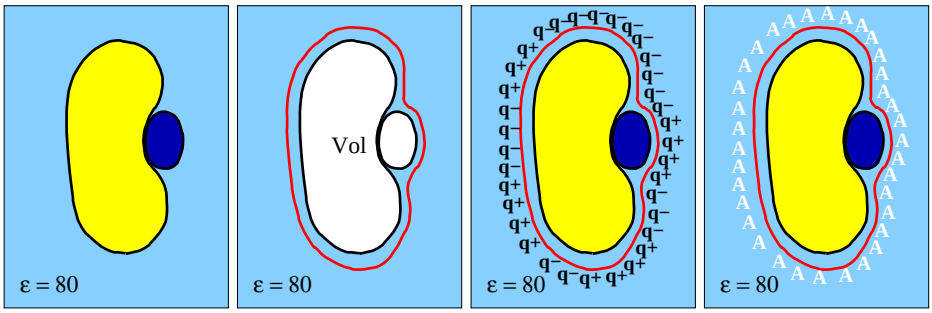

Figure 1. Elements of an Enhanced Implicit Solvation Model. a) Leftmost panel: A protein (yellow) in complex with some ligand (blue) resides in water considered as a dielectric continuum (light blue background). b) Second panel to the left: Formation of the boundary (red line) delivers the molecular surface and the molecular volume which in turn gives access to ΔG^{cav}. c) Second last panel to the right: Solution of the Poisson Boltzmann equation delivers a set of induced surface charges that allow calculation of ΔG^{pol}. d) Rightmost panel: Evaluation of response vector functions on the dielectric interface with appropriate Caillet-Claverie dispersion coefficients give access to an estimate of ΔG^{dis}.

2 Methods

2.1 System Set Up

Consider a protein (with potentially complexed ligand) in aqueous solution (see leftmost panel in Figure 1). The first thing to accomplish within our enhanced implicit solvation model will be the definition of a dielectric interface where the dielectric constant will abruptly switch from ε = 1 (protein interior) to ε = 80 (solvent continuum). Due to the intended advantageous description restricted to the solute-solvent boundary[4] the first step will comprise computation of the molecular surface and the molecular volume depicted as white area enclosed by a red line in Figure 1, second panel to the left. At first glance this might appear a trivial task, but in practice it turns out to represent a very crucial process with significant influence on overall performance and accuracy. A systematic study for a diverse set of structures using a variety of commonly employed molecular surface programs is currently underway in our group. The essential ingredients computed here are, boundary element location, size and corresponding normal vector, the net molecular surface area and the net molecular volume. All this implies prior assignment of AMBER charges and van der Waals radii.

2.2 Calculation of ΔG^{cav}

Having access to the molecular volume, or more specifically to the solvent excluded molecular volume (see second panel to the left in Figure 1), will enable us to derive an effective radius, $B_{eff} = \left(\frac{3}{4\pi} V^{slv.xcl}\right)^{\frac{1}{3}}$, that may be used in formulas of the *revised Pierotti Approach*[5]. Here a set of expansion coefficients, k_0, k_1, k_2, was derived from Free Energy Perturbation Calculations based on Molecular Dynamics Simulations of molecular liquids (see Table 1 in reference[5]).

2.3 Calculation of ΔG^{pol}

The major computational effort will be devoted to calculation of the polarization term. This is in fact the only one term considered in many other solvation models. The problem may be efficiently solved within the *Boundary Element Method*[6]. Here a set of surface charges is derived from the assumption that the change in the normal component of the electric field at the dielectric boundary cannot become discontinuous. Taking into account these additional surface charges to the original set of partial charges of the protein will allow an estimation of the polarization term, ΔG^{pol} (see second last panel to the right in Figure 1). The problem may be efficiently solved from an iterative solution scheme using specialized computer hardware[7].

2.4 Calculation of ΔG^{disp}

Similar to the electrostatic solute-solvent interaction an attractive van der Waals contribution can be obtained. Within the surface integral description the approach of Floris et. al. became well known[8]. Therefore we want to follow this strategy and calculate response vector functions A_i from re-parameterized Caillet Claverie parameters[9] (see rightmost panel in Figure 1). These critical dispersion coefficients may nowadays be determined from ab-inito calculations as outlined by Amovilli et. al.[10].

3 Concluding Remarks

Upon splitting the overall solvation free energy ΔG^{solv} into individual physical contributions and getting separate parameterizations for each of them independently, a rather solid description of environmental effects should arise. Work towards all of the described terms is currently in progress in our lab.

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